matter of this claim in a later-filed application and amended claims 1 and 36-37. Support for these amendments may be found *inter alia* in the specification as follows: claim 1: page 4, lines 7-9; claim 36: page 5, lines 8-9; claim 37: page 5, lines 6-7. Claims 1 and 36-37 do not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 1, 3-4,11-12 and 34-37 will be pending.

Rejection Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 1, 3-5, 11, 12 and 34-37 as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the above rejected claims, i.e. claims 1, 3-5, 11, 12 and 34-37 are **not** indefinite.

Claim 1

The Examiner alleged that Claim 1 is vague and indefinite for the following reasons: first, claim 1 has been amended to replace the phrase, "is transfected with DNA encoding", with "**overexpresses**" (emphasis added). The Examiner alleged that it is now unclear if the cells are overexpressing endogenous receptor for advanced glycation end product (RAGE) and mutant presenilin-2 protein, or if the cells require transient or stable transfection with vector(s) comprising cDNAs encoding RAGE and/or mutant presenilin-2. Second,

the Examiner stated that claim 1 step (c) recites the limitation "**cell culture**" (emphasis added). The Examiner alleged that there is insufficient antecedent basis for this limitation in the claim, because there is no prior recitation of "cell culture". Additionally, the Examiner stated that claim 1, step (d) recites, "comprising the level of cell death determined in step (c) with **amount** determined..." (emphasis added). The Examiner alleged that it is unclear to what the term "amount" is referring (i.e. the amount of what?). The Examiner alleged that Claims 3-5, 11, 12, and 34-37 depend upon claim 1 and are therefore rejected for the same reasons.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 1.

In support, claim 1 step (a) now recites in-part "contacting a cell which **expresses** (i) a receptor for advanced glycation end product (RAGE) protein and (ii) a mutant presenilin-2 protein with the compound" Therefore, claim 1 step (a) no longer recites the allegedly unclear term "**overexpresses**". Further, claim 1 step (a) has been amended to recite in-part "wherein the cell is in **a cell culture**". Therefore, there is sufficient antecedent basis for the alleged limitation of claim 1 step (c) which recites in-part "**the cell culture**". Further, claim 1 step (d) now recites "comparing the level of cell death determined in step (c) with the **level of cell**

death determined in the absence of the compound so as to evaluate the ability of the compound to inhibit neurotoxicity" (emphasis added). Therefore, claim 1 step (d) no longer recites the allegedly unclear term "**amount**". Accordingly, applicants contend that amended claim 1 steps (a) and (d) obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim 5

The Examiner alleged that claim 5 is vague and indefinite because it is unclear if the cells are transiently or stably transfected with a vector comprising cDNA encoding mutant presenilin-2 or if endogenous mutant presenilin-2 protein is "overexpressed" in the cells. The Examiner alleged that the term "overexpressed" implies that mutant presenilin-2 protein is expressed at a greater than basal level in the cells. The Examiner alleged that it is unclear if there is any basal level of mutant presenilin-2 protein expression in the cells. The Examiner alleged that it is unclear how the term "overexpressed" would differ from "expressed" when used to describe the expression of mutant presenilin-2 in the cells. The Examiner alleged that any expression of mutant presenilin-2 protein could therefore be considered overexpression.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claim 5.

Applicants contend that canceled claim 5 obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claims 36 and 37

The Examiner stated that Claims 36 and 37 recite the limitation "DNA". The Examiner alleged that there is insufficient antecedent basis for this limitation in the claim because there is no recitation of "DNA" in claim 1.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claims 36-37.

In support, claim 36 now recites "the method of claim 1, wherein the cell expresses human RAGE." Therefore, claim 36 no longer recites the alleged limitation "DNA". In addition, Claim 37 now recites "the method of claim 1, wherein the cell expresses N141 mutant presenilin-2." Therefore, claim 37 no longer recites the alleged limitation "DNA". Accordingly, applicants contend that amended claims 36-37 obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 11 and 12 as allegedly containing

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner alleged that Claim 11 is drawn to a pharmaceutical composition which comprises a compound which inhibits neurotoxicity in a cell by inhibiting interaction between receptor for advanced glycation end product (RAGE) and mutant presenilin-2 identified by the method of claim 1, and a pharmaceutically acceptable carrier. The Examiner alleged that the claim encompasses a genus composed of all compounds that inhibit the interaction of RAGE and mutant presenilin-2. The Examiner alleged that the specification does not disclose a single species compound that inhibits the interaction of RAGE and mutant presenilin-2. The Examiner alleged that the disclosure is not deemed sufficient to reasonably convey to one skilled in the art that applicants were in possession of a compound that inhibits the interaction of RAGE and mutant presenilin-2 at the time the application was filed. The Examiner alleged that the written description requirement is not satisfied for the claimed genus. The Examiner stated that Claim 12 depends upon claim 11 and is therefore rejected for the same reason. The Examiner stated that the amendment filed on April 4, 2001 has been entered as requested by the applicants in the request for continued prosecution filed June 8, 2001. However, the Examiner stated that Applicants did not respond to the office action of May 10, 2001, wherein the rejection of claims 11 and 12 under 35 U.S.C. §112, first paragraph were maintained; therefore, the rejection of claims 11 and 12 under 35

U.S.C. 112, first paragraph is maintained for the reasons previously stated in the office action of May 10, 2001, a summary of which follows. The Examiner maintained as stated in the previous Office Actions that the specification allegedly does not disclose compounds encompassed by the claimed pharmaceutical compositions which inhibit neurotoxicity, and further, the state of the art at the time of filing teaches that providing a pharmaceutical composition for treating neurological disorder is neither routine nor predictable (see, e.g., page 6 of the Office action of 10/2/00, Paper No. 11, and pages 5-7 of the Office action of 1/3/00, Paper No. 9).

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 11.

In support, claim 11 now recites as follows: "A pharmaceutical composition which comprises a compound which inhibits neurotoxicity in a cell which expresses receptor for advanced glycation end product (RAGE) and mutant presenilin-2 identified by the method of claim 1, and a pharmaceutically acceptable carrier." Therefore Claim 11 no longer recites the allegedly nonenabled language "**by inhibiting interactions between receptor for advanced glycation endproduct and mutant presenilin-2**." Applicants contend that amended claim 11 obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of

rejection.

Rejection Under 35 U.S.C. §103(a)

The Examiner stated that Claims 1, 3-5, 11, 12 and 34-37 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Wolozin et al. (Science, 274:1710-1713; December 6, 1996) taken with Yan et al. (Nature 328:685-691, 1996). The Examiner stated that Applicants' arguments filed April 4, 2001 have been fully considered but they are not persuasive. The Examiner alleged that the claimed invention is drawn to a method of evaluating the ability of a compound to inhibit neurotoxicity and pharmaceutical compositions comprising the compounds identified by the method. The Examiner alleges that there is motivation for one of ordinary skill in the art to combine Wolozin et al. and Yan et al. for the reasons stated in the previous Office Action dated October 4, 2000, a summary of which follows. The Examiner alleges that Wolozin et al. disclose expressing presenilin-2 or mutant presenilin-2 (e.g. N141I) in PC12 cells and treating the cells with amyloid-β results in increased apoptosis compared to untransfected controls (see figure 4). In addition, the Examiner alleged that Wolozin et al disclose a method comprising a) culturing the neuronally differentiated PC12 cells in the presence or absence of a compoud, i.e., pertussis toxin or amyloid-β(1-42), b) determining the level of apoptosis in the control and treated cells, and c) comparing the extent of the apoptotic activity in the cells cultured in the presence of the compound compared to cells cultured in the absence of the compound to evaluate the effect of the compound on apoptotic activity (see, e.g., page 1713, note #21). The Examiner stated

that while Wolozin et al does not disclose adding nucleic acid compound to neuronally differentiated PC12 cells expressing a mutant presenilin-2 protein, or all of the claim-designated pharmaceutical carriers, Wolozin et al does allegedly disclose adding PS-2 or ALG-3 antisense nucleic acids to neuronally differentiated PC12 cells which do not express a mutant presenilin -2 protein. The Examiner alleged that addition of the antisense nucleic acid results in a decrease in apoptotic activity in the PC12 cell (see, e.g., page 1720, middle and right columns, Figure 1). The Examiner alleged that inasmuch as Wolozin et al disclose that PC12 cells that express a mutant presenilin-2 protein have a high apoptotic activity, it would have been obvious to add PS-2 or ALG-3 antisense nucleic acids to neuronally differentiated PC12 cells expressing mutant presenilin-2 protein for the purpose of determining if the antisense nucleic acids are effective in decreasing the observed apoptotic activity in PC12 cells expressing mutant presenilin-2 protein. The Examiner alleged that adding the nucleic acids, or other compounds such as pertussis toxin or amyloid-β(1-42) to cell cultures as a pharmaceutical composition would have been obvious and well within the purview of one of ordinary skill in the art of cell culture. The Examiner alleged that one of ordinary skill in the art would have been motivated to admix the compound of interest with a suitable carrier to more easily control the concentration of the compound added to the cell culture to avoid a localized high concentration of a solid compound which may be detrimental to the cells. The Examiner stated that Wolozin et al do not teach that the PC12 cells are transfected with

a DNA sequence encoding RAGE and which is transfected in PC12 cells. However, the Examiner alleged that Yan et al teach that enhanced expression of RAGE in Alzheimer's disease, in affected neurons, in microglial and in vasculature, is consistent with the concept that amyloid-β-RAGE interaction may contribute to neurotoxicity that results in dementia (see page 382, left column, last paragraph). Thus the Examiner alleged that it would have been obvious to one of ordinary skill in the art to provide cells associated with neurodegenerative disease, in a method of identifying compounds which inhibit neurotoxicities associated with neurodegenerative diseases. The Examiner alleged that Yan et al further teach that human amyloid-β(1-40 or 1-42) purified from plaques or vascular amyloid-β from Alzheimer's disease patients inhibits binding of amyloid-β-induced cellular perturbation results in oxidant stress and cytotoxicity (see, e.g., p 688 right column, under "RAGE and amyloid-β-induced cellular stress"). The Examiner alleged that Yan et al indicate that RAGE can mediate amyloid-β induced oxidant stress on endothelium and neuronal cells and that the stress can be prevented by blocking access to RAGE using either anti-RAGE IgG or excess soluble receptor, and further teach that expression of RAGE increases vulnerability to ayloid-β. The Examiner alleged that Yan et al indicate that RAGE, if present and/or upregulated in cells important in the pathogeneis of Alzheimer's' disease, could mediate toxic effects when associated with amyloid-β. The Examiner alleged that Yan et al teach transfection of RAGE into COS-1 cells and the use of these transfected cells in analyzing the effect of compounds on amyloid-β

activity with respect to oxidant stress (see, e.g., p688 under "RAGE and amyloid-β-induced cellular stress). The Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time of the claimed invention was made to modify the method of Wolozin et al by further modifying the presenilin-2 transfected PC12 cells of Wolozin et al by transfecting the cells with a vector encoding RAGE in view of the teachings of Yan et al. that cells transfected with RAGE are useful in studying the interaction of RAGE and amyloid-β-on oxidant stress and cytotoxicity in cells. The Examiner alleged that one of ordinary skill in the art would have been motivated to provide such a modified PC12 cell to use in a method of identifying inhibitors of neurotoxic compounds, such as those associated with Alzheimer's disease, in view of the teachings of Yan et al that enhanced expression of RAGE in Alzheimer's disease, in affected neurons, in microglial, and in vasculature, is consistent with the concept that amyloid-β-interaction may contribute to neurotoxicity that results in dementia. The Examiner stated that although there was no indication in either Wolozin et al or Yan et al. that an interaciton between amyloid-β and presenilin-2 exisited, it would have allegedly been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Wolozin et al. that overexpression of presenlin-2 and mutant presenilin-2 protein in PC12 cells increases the cells sensitivity to amyloid-β neurotoxicity with the teachings of Yan et al that overexpression of RAGE in neuronal-associated cells of increases the cells sensitivity to amyloid-β neurotoxicity for the purpose of creating cells that have a greater

sensitivity to amyloid-β neurotoxicity for the purpose of identifying compounds that inhibit neurotoxicity. Thus, the Examiner alleged that the claimed invention was obvious at the time the claimed invention was made in view of Wolozin et al. taken with Yan et al.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that it would not have been obvious to one of skill in the art to combine mutant PS2 with RAGE to create the present invention because the prior art references do not demonstrate or suggest any interaction between mutant PS2 and RAGE necessary for identifying and testing neuroprotective therapeutics. Therefore, the prior art references do **not** provide a suggestion or motivation to modify the reference teachings to produce the claimed invention. Accordingly, the claimed invention was not obvious in view of Wolozin et al. taken with Yan et al.

In support, the present invention teaches an interaction between mutant presenilin-2 and RAGE. The specification recites that "while mutant presenilin-2 by itself has little effect on apoptosis, cells co-transfected to express mutant presenilin-2 and RAGE showed a dramatic increase in apoptosis at Aβ concentrations of both 0.3 and 1μM." See page 23, lines 9-13. Further, the specification recites that "as mutant presenilin and elevated levels of RAGE are both associated with AD, the interaction of these two molecules, either directly or indirectly, might greatly augment Aβ toxicity." See page 20, lines 1-4. Further, the

specification recites that "the synergistic interaction of these two factors (mutant PS2 and RAGE) resulted in dramatically increased apoptosis." See page 23, lines 25-27. In addition, the specification recites that "the interaction of mutant presenilin-2 with RAGE in transfected cultured cells, and as well as in transgenic mice, provides a useful model system for identifying the pathobiology of AD and as a model for identifying and testing neuroprotective therapeutics. Accordingly, the specification teaches that the synergistic interaction between mutant presenilin-2 and RAGE in neuronal cell lines mimic the pathobiology of AD and provide a model for identifying and testing neuroprotective therapeutics.

In contrast, Wolozin et al. recite that "overexpression of the familial Alzheimer's disease gene Presenilin 2(PS2) in nerve growth factor-differentiated PC12 cells increased apoptosis by trophic factor withdrawl or β-amyloid." See page 1710, abstract. Accordingly, while Wolozin et al. may at most teach a role for presenilin-2 in apoptosis it fails to demonstrate or suggest any relationship between mutant presenilin-2 and RAGE as disclosed in the present invention. In addition, Yan et al. recite that "Aβ binding to RAGE and Aβ-induced cellular perturbation resulted in oxident stress and cytotoxicity." Therefore, while Yan et al. may at most teach a role for RAGE and Aβ peptide in neurotoxicity, it does not demonstrate or suggest any use of RAGE and presenilin-2 necessary for one of skill in the art to produce the claimed invention. Accordingly, the claimed invention was **not** obvious in

view of Wolozin et al. taken with Yan et al.

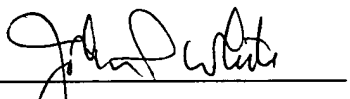
Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $460.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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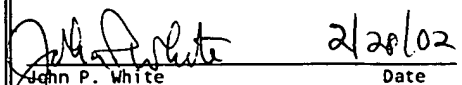
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



2/28/02
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